

National Institute of Allergy and Infectious Diseases / Division of Microbiology and Infectious Diseases	<b>Policy</b> <b>Development of Criteria for Volunteer Participation in DMID Clinical Research</b>	No.: DMID Policy-007 – NCRS 1.2 v4.0
	Effective Date: 13-JUL-2016	Version: 4.0

## 1.0 Purpose:

The Division of Microbiology and Infectious Diseases (DMID) commissions/funds clinical research protocols to answer clinical research questions. This policy provides guidance for the development of protocol-defined criteria in the selection of volunteers. The policy also provides guidance for the development of protocol-defined criteria for continuation of volunteer participation in human subject research.

## 2.0 Scope:

This policy applies to DMID staff, investigators, study staff, and advisory committees involved in protocol development and execution of DMID-supported clinical research. The policy does not supersede protocol-defined language.

## 3.0 Policy:

Volunteers must meet protocol-defined criteria for enrollment in a given study and must continue to meet protocol-defined criteria for ongoing participation in a study. Ongoing participation includes all possible protocol paths including screening, pre-dosing time periods, active dosing regimens, safety follow-up, and safety follow-up of volunteers who are no longer eligible to receive study interventions.

The protocol must describe protocol-defined laboratory, physiologic, or other parameters necessary to evaluate the volunteer's general health status. Toxicity tables or other grading structures and acceptable baselines for protocol-defined safety parameters should be included in the protocol, as appropriate. All protocol-defined parameters must be in the ranges defined by the protocol in order to enroll a volunteer into the study.

Abnormal values for ancillary laboratory tests that do not meet protocol halting rules or do not require withdrawal of the volunteer need to be reviewed. If, in the opinion of the investigator and as described in the protocol, these ancillary laboratory test abnormalities do not add additional concerns for volunteer safety or study data interpretation, the volunteer may receive the intervention in accordance with the conditions and procedures defined in the protocol. Principal Investigators (PIs) are encouraged to consult with DMID for questions on the inclusion and continuation of specific volunteers.

## 4.0 Background

DMID and its sponsored investigators/institutions must meet the requirements of the Code of Federal Regulations 45 CFR 46, Protection of Human Subjects, and, as applicable, 21 CFR 11, 50, 54, 56, 312 and 812. Protocols need to adequately address the safety of volunteers participating in the study and meet an acceptable risk-benefit ratio for the proposed study. Protocol-defined laboratory tests and physiologic parameters provide objective evidence of the health status of the research volunteer and are intended to ensure the protection of human subjects' safety and the integrity and reliability of the study. Health is a continuum that can be defined on many different parameters, axes, and/or scales. The goal of the investigator, sponsor, and protocol is to provide an adequate description of the study to determine if the health of the volunteer is appropriate for participation in the study.

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Individuals are invited to participate in NIAID clinical research and clinical trials. After accepting this invitation, the process of determining the volunteer's appropriateness for a trial can begin. This process hinges on volunteers continuing to accept the invitation as they learn more details about the research. This process also relies on the interaction between the site staff, the volunteer, and the requirements of the protocol.

Criteria for volunteer participation should be developed that are appropriate for the phase of the study and should include both general and product-specific safety parameters. For early studies where there are limited product safety data, the criteria should be more stringent to attempt to minimize risks, and increase the understanding of potential risks of the intervention. For products with known safety signals, the criteria should reflect those known risks. As a safety database expands, eligibility criteria for volunteer participation should be re-evaluated as appropriate. By being as inclusive as possible and practical, the clinical trial has the best chance to predict the performance of the product(s) in a general population. The decision to include a volunteer involves several different but somewhat convergent factors: protocol design, eligibility criteria, the safety of the volunteer, known and suspected toxicities of the intervention, and interpretation of protocol results.

If the study intends to enroll defined populations that require special considerations and additional protections such as children, pregnant women, or prisoners, applicable sections of 45 CFR 46 must be followed.

## 5.0 Definitions:

**Ancillary Laboratory Tests:** Tests not defined in the protocol. Results of an ancillary laboratory test may be obtained as part of a panel of tests.

**Clinical Research:** NIAID human subjects term indicating research conducted on human subjects or on material of human origin that can be personally identified. Policy covers large and small-scale, exploratory, and observational studies. There are three types: Patient-oriented research (investigators directly interact with study participants); epidemiologic and behavioral studies; outcomes and health services research. This term applies to both clinical trials and clinical studies.

**Clinical Study:** Clinical research that does not meet the definition of a clinical trial.

**Clinical Trial:** A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

**Human Subjects:** Legally defined term for living persons from or about whom an investigator obtains specimens or data through direct interaction or intervention or through identifiable, private information.

**Protocol-Defined Parameters:** Protocol-defined values, including laboratory tests, clinical assessment, specialized testing, and/or diagnosis specified in the protocol.

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**Volunteer:** A person who, by his/her own free will, undertakes or expresses a willingness to undertake a service without obligation. In human subject research, this individual presents for consideration and/or consents to participate in human subjects research.

## 6.0 Implementation:

The following provides general guidance for consideration during protocol development. The protocol should describe the specific implementation of the study objectives as applicable to the specific product and volunteer population. DMID will continue its long held position of allowing no exceptions to the protocol-defined eligibility criteria.

### 6.1 Clinical Assessment

The protocol should define which volunteers are eligible for enrollment and continuation for each of the following.

- 6.1.1 General and specific inquiries about medical history should be made, including inquiries relevant to specific eligibility criteria. Appropriate information obtained from volunteers and/or medical records should be documented. A discussion between the DMID protocol team and the clinical investigators about appropriate history questions should take place during protocol development.
- 6.1.2 Acute Transient Conditions: Human health can change both rapidly and transiently. If there is a plausible alternative explanation for an abnormal protocol-defined criterion (e.g., laboratory values, vital signs, physical exam), the volunteer may be retested to see if the value/parameter returns to a defined range. DMID permits one repeat testing to confirm a plausible alternative explanation unless otherwise specified in the protocol. See also section 6.3.
- 6.1.3 Acute or Episodic Medication: Volunteers who take medications for relief of transient symptoms or acute disease/conditions or flares may be included. Volunteers who have a consistent or predictable history of medication taking or disease/conditions that would impact an important protocol outcome should be excluded. Volunteers taking medication(s) that need frequent adjustment or have major known adverse events would need careful consideration prior to enrollment into a study, (e.g., triptans, Epipen®).
- 6.1.4 Common Health Conditions: Volunteers with chronic conditions that are well managed with predictable and/or occasional breakthrough may be included if appropriate for the particular trial.
- 6.1.5 Chronic Medications: Chronic medications may include vitamins, health supplements, herbal preparations, contraceptives, or other prescription or non-prescription medications likely to be taken during the volunteer's participation in the protocol to preserve health or prevent initiation or progression of disease. Volunteers on chronic medication that has no impact on the trial's outcome may be included. Chronic medication regimens that require frequent adjustment or have major known adverse events would require careful consideration prior to enrollment into a study, (e.g., warfarin, insulin).

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- 6.1.6 Vital Signs: If vital signs are taken, acceptable ranges should be defined in the protocol.
- 6.1.7 Weight: A range of body mass index (BMI) or other age appropriate weight percentiles that are acceptable should be defined in the protocol.
- 6.1.8 Physical Exam: The protocol should define the elements/extent of the physical exam.
- 6.2 Laboratory Assessment
  - 6.2.1 Laboratory Criteria
    - 6.2.1.1 Eligibility Labs: The protocol must specify appropriate eligibility criteria for the study. Acceptable laboratory values can consist of the laboratory normal values or alternative values defined in the protocol. The protocol must address how values that are obtained as part of a panel and not defined as part of the eligibility criteria will be handled. If a volunteer is enrolled with abnormal values obtained as part of a panel, these abnormal values must be addressed in the protocol and the documents supporting the enrollment decision and rationale must be available for DMID review.
    - 6.2.1.2 Safety Labs: Safety labs are protocol-and product-specific. These values must be graded by protocol specific toxicology tables. The protocol must specify how values that are obtained as part of a panel and not part of the prescribed safety lab will be handled. If a volunteer is allowed to continue with abnormal values obtained as part of a panel, these accepted values must be defined in the protocol. These values and the documents supporting the continuation decision and rationale must be available for DMID review.
  - 6.2.2 Specialized Testing and Diagnosis
    - 6.2.2.1 If a protocol requires specialized testing or diagnosis, specific guidelines for interpretation must be described in the protocol. The protocol must identify which test is to be performed, what information will be transmitted to the PI, and what criteria will be used for eligibility.
- 6.3 Retesting: In the case where a parameter is outside of the acceptable limits for enrollment, measurement of the parameter can be repeated one time if both the following are met:
  - 1. In the opinion of the investigator, the parameter value does not represent a chronic condition that otherwise will preclude the volunteer from enrolling in the study; and
  - 2. In the opinion of the investigator, the abnormality is not likely to recur.
- 6.4 Nothing in this document should be interpreted as limiting the prerogative of the PI to exclude individuals from participation based on information that is not specifically listed as an exclusion criterion. If there are ambiguities in protocol requirements for either entry criteria or execution, the PI may seek guidance from the DMID as to the intent. This guidance can come from the assigned Scientific Lead, Clinical Project Manager, Medical Officer, Medical Monitor, or Regulatory Affairs Specialist, as appropriate. As ambiguities in the protocol might

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necessitate a protocol amendment, ambiguities ideally should be identified and corrected during protocol development.

## 7.0 References:

### 7.1 US Code of Federal Regulations

- 7.1.1 [45 CFR 46, Protection of Human Subjects](#)
- 7.1.2 [21 CFR 11, Electronic Records; Electronic Signatures](#)
- 7.1.3 [21 CFR 50, Protection of Human Subjects](#)
- 7.1.4 [21 CFR 54, Financial Disclosure by Clinical Investigators](#)
- 7.1.5 [21 CFR 56, Institutional Review Boards](#)
- 7.1.6 [21 CFR 312, Investigational New Drug Application](#)
- 7.1.7 [21 CFR 812, Investigational Device Exemptions](#)

### 7.2 [DMID Policies, Guidances, and Tools public web site](#)

### 7.3 [International Conference on Harmonization \(ICH\) E6: Good Clinical Practices](#)

## 8.0 Inquiries:

Questions or comments regarding this policy may be directed to:

Associate Director for Clinical Research  
Division of Microbiology and Infectious Diseases (DMID)  
NIH / NIAID  
5601 Fisher Lane Rm. 7E60  
Bethesda, MD 20892  
[DMIDPolicyQuery@mail.nih.gov](mailto:DMIDPolicyQuery@mail.nih.gov)

## 9.0 Availability:

This policy is located electronically on the NIAID/DMID website at:

<http://webedits.niaid.nih.gov/labsandresources/resources/dmidclnrsrch/Pages/studyvolunteers.aspx>

## 10.0 Change Summary:

Version Number	Date of Revision: DD-MMM-YYYY	Replaces	Effective Date: DD-MMM-YYYY	Description of Revision/Retirement
1.0	N/A	DMID.PD.001R: DMID Acceptable Methods for Determining Eligibility for Healthy Volunteers	16-APR-2012	N/A
2.0	18-JUL-2013	Version 1.0	01-AUG-2013	Annual renewal; Administrative edits
3.0	05-AUG-2014	Version 2.0	15-AUG-2014	Clarify retesting conditions
4.0	17-JUN-2016	Version 3.0	13-JUL-2016	Updated clinical trial definition; Administrative